NATIONAL GUIDELINE CLEARINGHOUSE™ (NGC™)
GUIDELINE SYNTHESIS

Use of Colony Stimulating Factors in Patients Receiving Chemotherapy

Guidelines

1. American Society of Clinical Oncology (ASCO). Recommendations for the use of hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines. J Clin Oncol 1994 Nov;12(11):2471-508; 1997 Update: J Clin Oncol 1997 Oct;15(10):3288. 2000 Update: J Clin Oncol 2000 Oct;18(10):3558-85.
2. *Practice Guidelines Initiative (PGI). Use of granulocyte colony-stimulating factor (G-CSF) in patients receiving myelosuppressive chemotherapy for the treatment of cancer. Cancer Prev Control 1998;2(4):179-90.
CURRENT NGC SUMMARY: Use of granulocyte colony-stimulating factor (G-CSF) in patients receiving myelosuppressive chemotherapy for the treatment of cancer.

*Please note: Practice Guidelines Initiative (PGI) has updated its guideline. The National Guideline Clearinghouse is working to update this synthesis and will post the update as soon as possible.

INTRODUCTION

A comparison of ASCO and CCOPGI recommendations for the use of granulocyte colony-stimulating factor (G-CSF) in preventing or treating chemotherapy-induced febrile neutropenia and infectious complications is provided in the following table. During development of their guideline, CCOPGI considered the recommendations of other evidence-based guidelines, including those from ASCO.

Abbreviations: ASCO, American Society of Clinical Oncology; CCOPGI, Cancer Care Ontario Practice Guidelines Initiative; CSF, colony-stimulating factors; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte macrophage colony-stimulating factor.

	ASCO (1994, updated 2000)	**CCOPGI (1997)**
OBJECTIVE AND SCOPE	• To establish evidence-based clinical practice guidelines for the use of	• To evaluate the evidence on the role of G-CSF in patients

	colony-stimulating factors (CSFs; referring to either G-CSF or granulocyte macrophage colony-stimulating factor, GM-CSF) in patients who are not enrolled in clinical trials. • To encourage reasonable use of hematopoietic CSFs to preserve effectiveness but discourage excess use when little marginal benefit is anticipated.	receiving myelosuppressive chemotherapy for the treatment of cancer.
INTENDED USERS	Oncologists	Oncologists
TARGET POPULATION	• Adults and children with cancer undergoing cytotoxic treatment (i.e., myelosuppressive chemotherapy, myeloablative chemotherapy and bone marrow transplant).	• Adult cancer patients receiving myelosuppressive chemotherapy.
INTERVENTIONS AND PRACTICES CONSIDERED	Prophylactic and therapeutic use of hematopoietic colony-stimulating factors (CSFs) CSFs commercially available in the United States: • Granulocyte colony-stimulating factor (G-CSF; filgrastim; *Escherichia coli*-derived G-CSF; Neupogen [Amgen, Thousand Oaks, CA]) • Granulocyte-macrophage colony-stimulating factor (GM-CSF; sargramostim; yeast-derived GM-CSF; Leukine [Immunex, Seattle, WA]) CSFs under development in	Prophylactic and therapeutic use of G-CSF. GM-CSF is not considered.

	the United States: • GM-CSF (molgramostim; *E. coli* derived GM-CSF Leucomax [Schering-Plough, Madison, NJ and Sandoz, E. Hanover, NJ]) CSFs developed primarily outside the United States: • Lenograstim (G-CSF) • Regramostim (GM-CSF) • Ecogramostim (GM-CSF)	
COMPARISON OF RECOMMENDATIONS FOR PROPHYLACTIC AND THERAPEUTIC USES		
To prevent neutropenia: • Primary prophylaxis for previously untreated patients receiving first cycle of chemotherapy. • Secondary prophylaxis for patients with documented occurrence of neutropenia during a previous cycle of chemotherapy.	• CSFs are recommended when the expected incidence of febrile neutropenia (based on the chemotherapy regimen) is greater than or equal to 40%. Thus, in general, for previously untreated patients receiving most chemotherapy regimens, primary administration of CSFs should not be used routinely. • Primary CSF administration may be exceptionally warranted in patients at higher risk (e.g., pre-existing neutropenia due to disease) for chemotherapy-induced infectious complications even though the data supporting such use is not conclusive. • Secondary prophylaxis: CSFs may be warranted for patients with a history of recurrent FN while receiving earlier chemotherapy of similar	If the objective of using G-CSF is to maintain dose-intensity of antitumour agents, then G-CSF can be recommended where reduction in dose-intensity has been shown in randomized controlled trials to reduce survival or disease-free survival. Although the evidence is weaker, the development group indicated support for the practice endorsed by other groups (ASCO, Ontario Drug Benefit Plan) and recommends G-CSF for patients receiving potentially curative chemotherapy as • Primary prophylaxis; that is, where dose reductions below a specified level are required because of a known high risk of febrile neutropenia. • Secondary prophylaxis in patients receiving chemotherapy of established efficacy who have suffered a prior serious episode of febrile neutropenia due to the same

	or lesser dose intensity or for patients with potentially curable cancers to maintain dose intensity in subsequent treatment cycles when chemotherapy dose reduction is not an option. However, in the absence of clinical data supporting maintenance of chemotherapy dose-intensity physicians should consider chemotherapy dose reduction as an alternative to the use of CSFs.	chemotherapy regimen. The exact cut-off for dose reductions is unknown at this time, and ought to be left to the judgment of the clinician. In general, the use of G-CSF for dose reductions less than 20% is not recommended.
To maintain chemotherapy dose-intensity in neutropenic patients	• In the setting of many tumors exclusive of curable tumors (e.g., germ cell tumors), dose reduction after an episode of severe neutropenia should be considered as the primary therapeutic option. No published regimens have demonstrated disease-free or overall survival benefits when the dose of chemotherapy was maintained and secondary prophylaxis was instituted. In the absence of clinical data or other compelling reasons to maintain chemotherapy dose-intensity, physicians should consider chemotherapy dose reduction after neutropenic fever or severe or prolonged neutropenia after the previous cycle of treatment.	• Although the evidence is weaker, the development group indicated support for the practice endorsed by other groups (ASCO, Ontario Drug Benefit Plan) and recommends G-CSF for patients receiving potentially curable chemotherapy in whom dose reductions below a specified level are required because of neutropenia. • The exact cut-off for dose reductions is unknown at this time, and ought to be left to the judgment of the clinician. In general, the use of G-CSF for dose reductions less than 20% is not recommended.
To treat neutropenia	• Afebrile neutropenia:	• If reduction in the

	Intervention with a CSF in afebrile neutropenic patients is not recommended. • Febrile neutropenia: CSFs should not routinely be used as adjunct therapy for the treatment of uncomplicated fever and neutropenia. Uncomplicated fever and neutropenia are defined as follows: fever of greater than 10 days duration; no evidence of pneumonia, cellulitis, abscess, sinusitis, hypotension, multiorgan dysfunction, or invasive fungal infection, and no uncontrolled malignancies. Clinical trials have consistently shown a decrease in the duration of neutropenia of less than 500/L, but clinical benefit has not consistently accompanied the decreased duration of neutropenia. • Certain patients (i.e., profound neutropenia [absolute neutrophil count less than 100/L], uncontrolled primary disease, pneumonia, hypotension, multiorgan dysfunction [sepsis syndrome], and invasive fungal infection) are at higher risk for infection-associated complications and have prognostic factors that are predictive of poor clinical outcome. The use of a CSF for such high-risk patients may be considered, but the benefits of a CSF in these circumstances have not been proven.	number of febrile neutropenic episodes or in the duration of such episodes is expected to improve quality of life, then G-CSF is a reasonable treatment option in selected patients. A clear justification for the use of G-CSF should be stated.

POTENTIAL HARMS ASSOCIATED WITH G-CSF		
Side effects of G-CSF	The predominant side effect associated with administration of G-CSF has been medullary bone pain. In randomized trials, 15% to 39% of patients receiving approximately 5 g/kg/d have described this symptom, compared with a 0% to 21% incidence in control patients. Less frequent side effects reported include exacerbations of preexisting inflammatory conditions, e.g., eczema, psoriasis, or vasculitis; rashes; allergic reactions; acute febrile neutrophilic dermatosis (Sweet syndrome); transient leukemia cutis, injection site reactions; mild alopecia; splenomegaly; splenic infarction; moderate reductions in platelet counts.	Toxicity of G-CSF is relatively mild. The most consistent clinical symptom attributed to G-CSF is bone pain reported in incidence rates ranging from 20% to 50% in three trials. With the exception of one case, reported bone pain was mild.

Guideline Content Comparison

The American Society of Clinical Oncology (ASCO) and the Cancer Care Ontario Practice Guideline Initiative (CCOPGI) present recommendations on the prophylactic and therapeutic use of G-CSF in cancer patients receiving myelosuppressive chemotherapy. Explicit rationale is provided for these recommendations.

ASCO also evaluates the evidence supporting the clinical use of GM-CSF, and presents recommendations, where possible, in the following areas that are not addressed by CCOPGI in their focused guideline:

- Use of CSFs to increase chemotherapy dose-intensity
- Use of CSFs as adjuncts to progenitor-cell transplantation
- Use of CSFs in patients with acute leukemia and myelodysplastic syndromes
- Use of CSFs in patients receiving concurrent chemotherapy and irradiation
- Use of CSFs in the pediatric population
- Dosing and route of administration
- Initiation and duration of CSF administration
- Comparative clinical activity of G-CSF and GM-CSF

CCOPGI plans to evaluate the use of G-CSF in patients undergoing bone marrow transplantation in a separate guideline.

Areas of Agreement

ASCO and CCOPGI agree that CSFs are not indicated as a routine prophylactic or therapeutic intervention in cancer patients receiving myelosuppressive chemotherapy.

CCOPGI revealed they considered the recommendations of other evidence-based guidelines, including those from the American Society of Clinical Oncology, during development of their guideline. Despite the lack of high quality evidence on which to base recommendations, CCOPGI ultimately supported the practice endorsed by ASCO regarding use of G-CSF in specific circumstances. Both groups recommend CSFs for patients at risk for febrile neutropenia and possibly for patients who had an episode of febrile neutropenia in a prior chemotherapy cycle. CCOPGI recommends G-CSF for patients receiving potentially curable chemotherapy to avoid dose reductions below a specified level because of neutropenia. ASCO also considers CSFs as an option to maintain chemotherapy dose intensity in neutropenic patients, but considers dose reduction the primary therapeutic option for non-curable tumors.

There is agreement also that future clinical trials of CSFs should focus on survival, quality of life, and resource utilization.

Areas of Differences

ASCO and CCOPGI emphasize different rationale for using CSFs as prophylaxis. ASCO defines the clinical basis for primary prophylaxis in terms of the predicted incidence of febrile neutropenia based on observed rates in control groups in randomized controlled trials, reserving use of CSFs when the expected incidence exceeds 40%. CCOPGI discusses primary administration of G-CSF in the context of chemotherapy dose maintenance, recommending its use for cases where dose reductions below a specified level are not advisable due to demonstrated reduction in survival or disease-free survival in randomized controlled trials.

This Synthesis was prepared by ECRI on October 8, 1999 and modified on December 11, 2000. It has been reviewed by the guideline developers as of January 5, 2001.

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